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Crosslinking of graft coPolymerization alginate with acrylic acid for releasing drugs

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Abstract

In this paper, synthesis and application of a novel alginate-based hydrogel as control releasing drug systems was investigated.The synthesized hydrogel exhibited a pH-responsiveness character so that a swelling-collapsing pulsatile behavior was recorded at pHs 1.2 and 7.4.This behavior makes the synthesized hydrogels as an excellent candidate for controlled delivery of bioactive agents.Therefore,Bovine serum albumin (BSA) as a model drug was loaded into the hydrogels by soaking the gels in a pH 7.4 and 1.2 buffer solution at 37°C(human body temperature).The drug was released gradually in the pH 7.4 buffer solution rather than in the pH 1.2.The release value of drug from hydrogels at pH 7.4 was higher than that at pH 1.2 due to the electrostatic repulsion between carboxylate groups.

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Introduction

Synthesis and characterization of superabsorbent hydrogels is the main goal of the several research groups in the world. These materials are defined as hydrophilic, three-dimensional networks with ability to absorb large values of water, saline solution, or physiological fluids. The absorbed fluids are hardly removable even under some pressure. They are widely used in various applications such as hygienics, foods, cosmetics, and agriculture(Buchholz. 1994; Castal *et al.*,1990; Zhang *et al.*,2007; Richter *et al.*,2004). The properties of the swelling medium (e.g. pH, ionic strength and the counter ion and its valency) affect the swelling characteristics. SAPs responding to external stimuli such as heat, pH, electric field, chemical environments, etc, are often referred to as "intelligent" or "smart" polymers.Among these, pH-sensitive hydrogels have been extensively investigated for potential use in site-specific delivery of drugs to specific regions of the gastrointestinal tract and have been prepared for delivery of low molecular weight protein drugs. Therefore, these hydrogels have important applications in the field of medicine, pharmacy, and biotechnology(Zhou *et al.*,2011; Huash *et al.*,2010). In the recent past, drug delivery to the colon has gained increasing importance because the colon is an effective site for treatment of local colonic disorders. In addition, colonic drug delivery is also useful for systemic absorption of protein and peptide drugs because of the low activity of proteolytic enzymes in the colon.

Many systems such as time-dependent systems and pH-sensitive coating have been developed for colon-specific drug delivery. However, the major obstacle of these systems is associated with the colonic variation among different individuals and the transient variation of the local colonic region. Based on unique physiological characteristics of the colon, aromatic azo bond-containing pH-sensitive hydrogels have been investigated for colon-specific delivery(Zhou *et al.*,2011; Raghavendra *et al.*,2010). Swelling of such hydrogels in the stomach (lower pH value) is minimal due to the presence of carboxylic groups. The extent of swelling increases as the hydrogel passes down the intestinal tract because of increase in pH leading to ionization of the carboxylic groups.In the present report, to following synthesis of a novel alginate-based hydrogel, traping and releasing of bovine serum albumin were studied. The release behavior of drug *in vitro* from hydrogels was also evaluated.

Experimental

Materials

Sodium alginate (chemical grade, MW 50000) ,N,N'-methylene bisacrylamide (MBA, from Fluka), ammonium persulfate (APS, from Fluka), acrylic acid (AA, from Merck) with analytical grade were purchased and used without further purification. All other chemicals were also analytical grade. Double distilled water was used for the hydrogel preparation and swelling measurements.

Synthesis of Superabsorbent hydrogels

Synthesis of the hydrogel, H-alginte-g-PAcA, was carried out using APS as an initiator and MBA as a crosslinker in an aqueous medium. A general procedure for crosslinking graft copolymerization of AcA onto alginte was conducted as follows. alginate (0.50-1.50 g) was added to a three-neck reactor equipped with a mechanical stirrer (Heidolph RZR 2021, three blade propeller type, 300 rpm), including 40 mL doubly distilled water. The reactor was immersed in a thermostated water bath preset at desired temperature (35-70 ^{o}C). After complete dissolution of alginte,the initiator solution (0.01-0.40 g APS in 5 mL H_2O) were added to the mixture. After stirring for 10 min, certain amounts of 70% neutralized AcA (2.0-8.0 g in 5 mL H_2O) and MBA (0.05-0.20 g in 5 mL H_2O) were simultaneously added to the reaction mixture. After 60 min, the produced hydrogel was poured to excess non-solvent ethanol (200 mL) and remained for 3 h to dewater. Then ethanol was decanted and the product scissored to small pieces (diameter ~5 mm). Again, 100 mL fresh ethanol was added and the composite hydrogel was remained for 24 h. Finally, the filtered hydrogel is dried in oven at 60 ^{o}C for 10 h. After grinding, the powdered superabsorbent was stored away from moisture, heat and light.

pH-sensitivity

pH-sensitivity of the hydrogel was investigated in terms of swelling and deswelling of the final product at two basic (pH 7.4.0) and acidic (pH 1.2) solutions, respectively. Swelling capacity of the hydrogels at each pH was measured according to Equation 1 at consecutive time intervals (30 min).

$$ES(g/g) = \frac{Weight\ of\ swollen\ gel - Weight\ of\ dried\ gel}{Weight\ of\ dried\ gel}$$

Procedur loading drug in the hydrogels

The drug of Bovine serum albumin (BSA) was weighed accurately and dissolved in buffer solutions of pH 7.4 to make a 250 ml solution. Then the absorbance *(A)* of a series of standard with different concentrations (C) was determined at 280 nm with UV spectrophotometer.The dry hydrogels were immersed in 10 ml of 65 mg/ml BSA (pH 7.4) buffer solutions at 37°C for 48 hr. The hydrogels were then dried at 37°C in a desiccator at normal pressure until constant weight was reached(Zhou *et al.*,2011). The concentration of BSA in the solution was determined with an ultraviolet-visible spectrophotometer at 280 nm and the BSA loaded in the hydrogel sample was calculated with the standard equations of curves. The chemical structure of BSA is shown in Figure 1.

In vitro release of BSA from the hydrogels

The samples (0.1±0.0001 g) were placed into 50 mL of the release medium (simulated gastric and intestinal fluids, SGF and SIF, respectively) at different pH values (pH 1.2 or 7.4) at 37°C with agitation. At fixed time intervals, 1 mL of the release medium was removed using a syringe attached with a 0.45 μm Millipore filter and after suitable dilution, the concentration of released drug was measured spectrophotometrically (UV-1201, Shimadzu, Kyoto, Japan) at 280 nm with the standard equations of curves(Hoffman *et al.*,2002; Po.,1994).

Results and discussion

pH-responsiveness behavior of hydrogel

Since the synthesized hydrogel, H-alginate-g-PAcA, shows different swelling behaviors in acidic and basic pH solutions, we investigated the reversible swelling-deswelling behavior of this hydrogel in solutions with pH 1.2 and 7.4 (Figure 2). At pH 7.4, the hydrogel swells due to anion-anion repulsive electrostatic forces, while at pH 1.2, it shrinks within a few minutes due to protonation of the solfunate and carboxylate anions. This swelling-deswelling behavior of the hydrogels makes them as suitable candidate for designing drug delivery systems. Such on-off switching behavior as reversible swelling and deswelling has been reported for other ionic hydrogels(Branco *et al.*,2010).

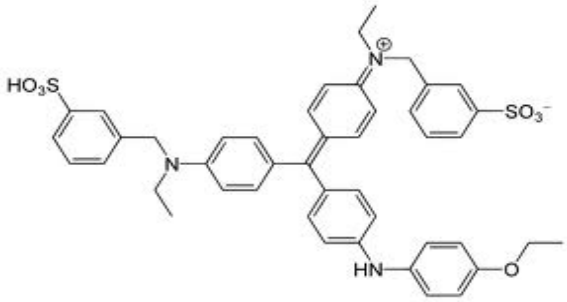

Fig. 1. Chemical structure of BSA.

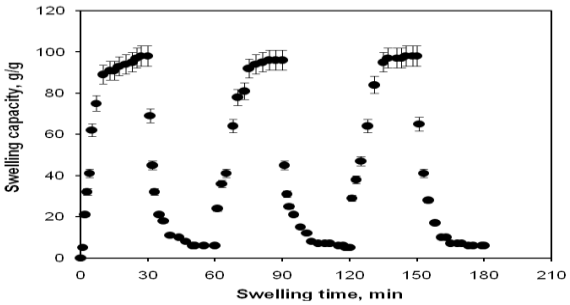

Fig. 2. On-off switching behavior as reversible pulsatile swelling (pH 7.4) and deswelling (pH 1.2) of the H-alginate-g-PAcA hydrogel.

Effect of pH on release drug

In order to investigate the effect of pH on the swelling of H-alginte-g-PAcA hydrogel we have measured the % cumulative release in both pH 1.2 and 7.4 media. Cumulative release data presented in Figure.3 indicate that by increasing the pH from 1.2 to 7.4, a considerable increase in the cumulative release is observed for H-alginte-g-PAcA hydrogel. This suggests that the drugs in the blend can be used to be suitable for the basic environment of the large intestine, colon, and rectal mucosa for which there

are different emptying times. Interestingly, more than 93 wt% drug is released from polymer at pH 7.4 within 30 hours, whereas less than 33 wt% of the drug is released at pH 1.2 within 30 hours. This suggests that the drugs in the H-alginte-g-PAcA hydrogel can be used to be suitable for the basic environment(Dai *et al.*,2007).

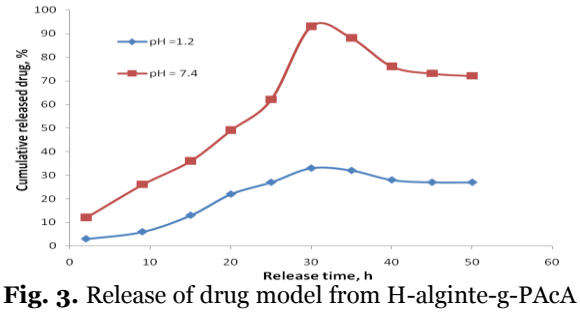

Fig. 3. Release of drug model from H-alginte-g-PAcA hydrogel carrier as a function of time in pH 1.2 and 7.4 at 37°C.

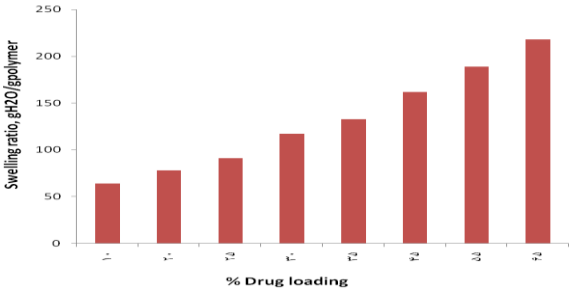

Fig. 4. water absorption of the H-alginte-g-PAcA hydrogel with different % drug loading.

Study loading and release BSA from hydrogels

To determine the potential application of alginate-based superabsorbent containing a pharmaceutically active compound, the drug release behavior form this system under physiological conditions was investigated.The dried gel samples (about 65 mg) were immersed in the pH 7.4 buffer solutions containing BSA at room temperature and allowed to swell at equilibrium. Then the gel samples were wiped by tissue paper to remove surface water and dried in vacuum at 60°C to a constant weight. The results of figure 4 indicated that the loading amount percent maximum of BSA was only %65 BSA. The main reason may be that since BAS is a macromolecule with large molecular size in comparison to the gel pore size, the loading levels achieved by this method are very limited.Here the percentage of swelling increases with increase in the percentage of drug loading in H-alginte-g-PAcA hydrogel(Dai *et al.*,2007; Wu *et al.*,2010).

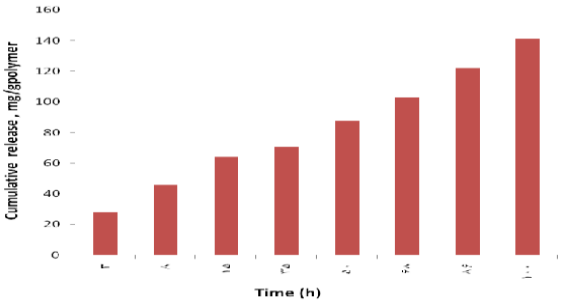

Fig. 5. In vitro release profile of BSA loaded in the H-alginte-g-PAcA hydrogel at 37°C.

In general, the permeability of hydrogel depends on factors such as the pore size of the hydrogel, the BSA size, and interactions between BSA and the gel network in water. Figure 5 shows the drug release from H-alginate-g-PAcA hydrogel loaded with BSA . It can be seen that BSA release is dominated by a small burst (before 35 h) followed by steady release (after 35 h). The burst release is due to the following reason (Wu *et al.*,2010).

Conclusions

In this paper, the swelling behaviour of hydrogel, H-alginate-g-PAcA, in various buffer solutions investigated.The superabsorbent hydrogels exhibited high sensitivity to pH. The reversible swelling-deswelling behavior in solutions with acidic and basic pH makes the hydrogels as a suitable candidate for controlled drug delivery systems. Therefore, BSA was used as the model protein to investigate the loading and release behavior of the hydrogels. The release value of drug from hydrogels at pH 7.4 was higher than that at pH 1.2 due to the electrostatic repulsion between carboxylate groups**.**

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